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Case Report

Nodular lymphocyte predominant Hodgkin's lymphoma of the cervix: A case report of a rare entity

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Introduction

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is an uncommon subtype of Hodgkin lymphoma (HL) (Morton et al., 2006). Extranodal involvement is a rare presentation of NLPHL (Shimabukuro-Vornhagen et al., 2005). In this report, we describe a case of NLPHL involving the uterine cervix in a 54-year-old woman who was treated with definitive radiation therapy (RT).

Case report

A 54-year-old healthy female, who has previously underwent subtotal hysterectomy with preservation of the cervix for treatment of uterine fibroids, presented with persistent vaginal bleeding. She has had two satisfactory Pap smears, dating 1 and 4 years prior to her presentation, both of which were negative for intraepithelial lesion or malignancy. Pelvic examination revealed a cervical mass. Endocervical curettage and a biopsy were performed and an enhanced computed tomography (CT) scan of the abdomen and pelvis was requested. The scan revealed enlargement of the cervix (Fig. 1(a)), associated with pelvic and inguinal lymphadenopathy.

Pathological examination of the endocervical curettage revealed lymphoid infiltration, consistent with a lymphoma (Fig. 2(a)). Despite the limited evaluation of the specimen due to its small size and fragmented nature, a nodular growth pattern was focally identified (Fig. 2(b)). On high magnification, the lymphoid nodules were populated by benign small lymphocytes, admixed with scattered large abnormal-appearing lymphoid cells with features highly suggestive of lymphocytic and histiocytic (L&H) Reed-Sternberg (RS) cells (Fig. 3). Immunohistochemical studies revealed that these cells were positive for CD20 (Fig. 4(a)), CD45, PAX5, BCL-6, BOB1 (Fig. 4(b)) and OCT2 (Fig. 4(c)). They were dimly positive or negative for CD30; no detectable expression for BCL-2, CD10, or CD3 and epithelial membrane antigen (EMA) was found. The background T cells were positive for CD3 and CD4, and a subset was positive for CD57. These large cells were rimmed with CD57-positive small T-cells. A good number of CD20-positive small B-cells were also found. Considering the overall morphological and immunophenotypic pattern, the diagnosis was felt to be NLPHL. In view of the unusual clinical presentation, a decision to obtain additional tissue biopsy was made. The repeat biopsy showed lymphoid cells arranged in a vaguely nodular pattern with scattered L&H cells. Rimming with CD3-positive T-cells was again noted (Fig. 4(d)). The remainder of the immunohistochemical studies revealed similar findings to those in the first biopsy. A diagnosis of NLPHL arising in the cervix was conferred.

A positron emission tomography (PET)-CT (Fig. 1(b)) revealed abnormal metabolic activity within the cervical mass, left inguinal lymph nodes (LNs) and bilateral common and external iliac LNs. Baseline blood investigations were unremarkable. The patient was designated Stage IIEA based on the Ann Arbour staging system. The treatment plan was discussed by our multidisciplinary lymphoma team and treatment with radiation alone was elected. The patient underwent CT simulation. The gross tumour volume (GTV) was defined as the disease identified on CT and PET-CT. The first clinical target volume (CTV1) included the cervix, para-aortic, bilateral common iliac, external iliac and inguinal LNs. This was treated to 40 Gy in 20 fractions using 15MV anterior and posterior photon fields, shielding normal structures when possible. The patient tolerated the treatment well and considerable response to RT was noted after 3 weeks, following which she underwent another CT simulation. Residual disease was limited to the cervical remnant and this constituted the CTV2 which was treated to an additional 10 Gy using 15 MV photons and a four-field box technique. Toward the end of the treatment, the patient developed grade 2 radiation dermatitis, grade 1 nausea and vomiting and grade 1 diarrhea.

The patient was clinically evaluated 2 months following the completion of RT when she was found to have recovered from radiation side effects. There was no evidence of residual disease but a 1.5 cm

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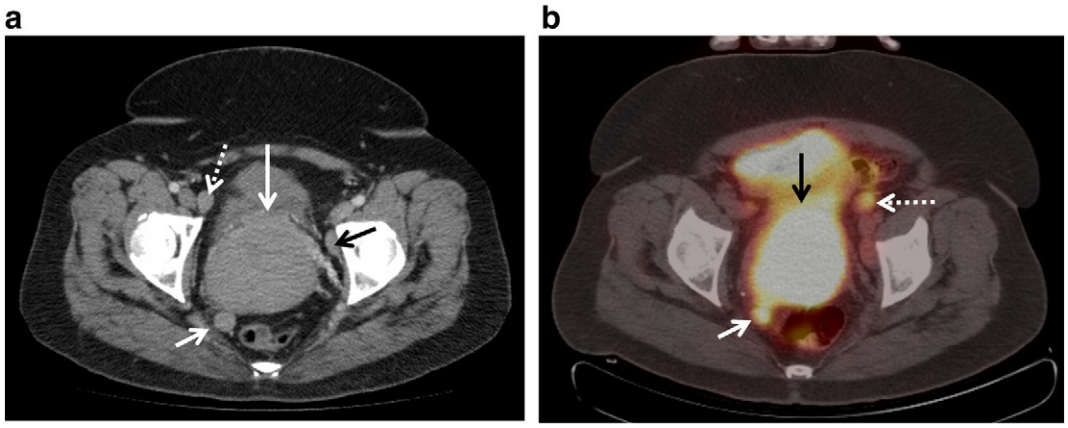

Fig. 1. (a) Contrast-enhanced computed tomography (CT) of a 54-year-old woman who presented with vaginal bleeding with remote history of subtotal hysterectomy with evidence of a large tumour of the residual cervix on pelvic examination. It shows an 8-cm cervical mass with smooth borders (solid long white arrow), a left external iliac lymph node (LN) (black arrow), a right external iliac LN (dashed white arrow), and a right internal iliac LN (solid short white arrow). (b) Positron emission tomography-CT scan showing increased metabolic activity in cervical mass (black arrow), a right internal iliac LN (solid white arrow) and a left external iliac lymph node (LN) (dashed white arrow).

necrotic ulcer in the vaginal vault consistent with the site of her previously large malignancy was observed. A CT scan of the chest, abdomen and pelvis also indicated complete response to radiotherapy. Subsequent evaluation, 5 months from RT, showed complete healing of the vaginal ulcer. The patient remains alive and in remission one and a half year since her diagnosis with no significant morbidity.

Discussion

NLPHL compromises 5% of all cases of HL, with classical Hodgkin lymphomas (CHL) being the more common subtype (IARC, 2008). It is a rare disease with an incidence of 0.08/100,000 people/year in the Unites States (Morton et al., 2006). The median age at diagnosis is 37 years and 75% of patients are males (Nogova et al., 2005).

Efforts to identify this morphologically distinct subtype of HL are worthwhile considering its different biological and clinical behaviors. Based on the most comprehensive comparison with CHL, NLPHL carries a more favorable prognosis (Nogova et al., 2008). The characteristic malignant cell, the lymphocytic and histiocytic (L&H) cell, is an atypical variant of Reed–Sternberg (RS) cell; L&H cells typically have vesicular, polylobulated nuclei and distinct small, peripheral nucleoli. The nuclear appearance resembles exploded popcorn, from which the term "popcorn cells" stems. These cells are present in a background of transformed follicles giving rise to the characteristic nodular architecture. Background cells consist of small B-lymphocytes, follicular dendritic cells, and follicular CD57 + T cells (IARC, 2008; Nogova et al., 2006). The characteristic L&H cells were identified in our patient but the nodular pattern was vague. However, a partly nodular pattern is considered adequate for establishing the diagnosis as per the WHO definition of NLPHL (IARC, 2008). Such as other lymphoma types, immunophenotyping plays a major role in establishing the diagnosis. The L&H cells are CD45 and BCL-6 positive and classically express B-cell antigens such as CD19, CD20, CD22, and CD79a. Unlike their counterparts, RS cells in CHL, these cells are usually negative for CD15 and CD30. The EMA, BOB-1, OCT-2 are positive in NLPHL and these supplementary markers aid establishing the diagnosis in difficult cases. Background T-cells are usually positive for CD3, CD4 or CD57 and the follicular dendritic cells are usually positive for CD21 and CD23 (IARC, 2008; Nogova et al., 2006). With the exception of CD21-, CD23-positive dendritic cells, the characteristic immunophenotypic pattern of NLPHL was reproduced in our patient.

Patients with NLPHL classically present with peripheral lymphadenopathy, with the neck being the most commonly involved site. Mediastinal involvement is rare. Splenomegaly is seen in 8% of patients and involvement of organs such as the liver, bone marrow, lungs or skeleton occurs in <5% (2). In our patient, the primary disease bulk was extranodal and to our knowledge, no cases of NLPHL of the cervix have been previously reported in the literature. Mihaljevic et al. reported a case of 69-year-old female who developed a relapse of CHL, a nodular sclerosis subtype, in the cervix. The patient initially presented with disseminated disease and was treated with chemotherapy followed by extended-field (EF) RT. She remained in complete remission for 15 years but then the disease recurred with solitary

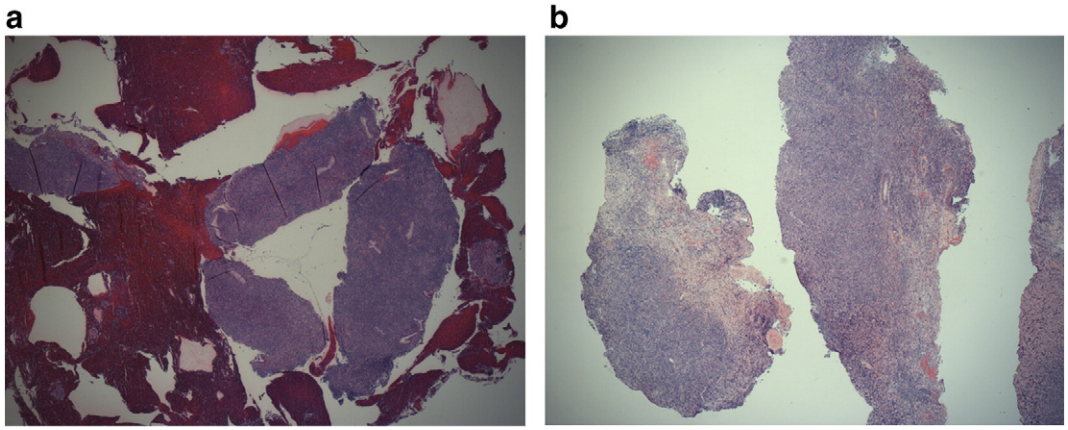

Fig. 2. (a) Endocervical curettage showing cervical glands surrounded by a dense lymphocytic infiltrate (haematoxylin and eosin ×100). (b) Focally, a vaguely nodular growth pattern of the lymphoid cells was noted (haematoxylin and eosin ×100).

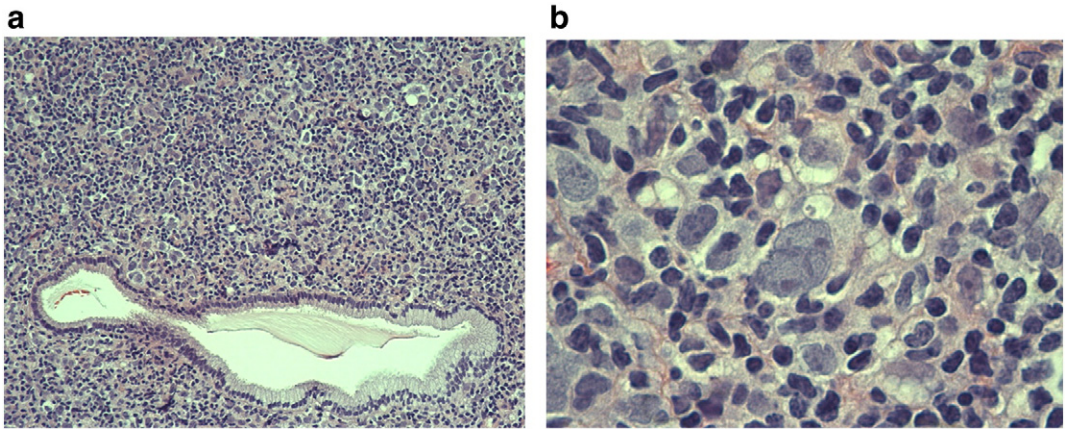

Fig. 3. (a) Uterine cervix biopsy showing a cervical gland surrounded by a mixture of large lymphoid cells and benign-appearing small lymphocytes (haematoxylin and eosin ×400). (b) Uterine cervix biopsy showing the presence of large abnormal-appearing lymphoid cells with polylobulated nuclei (popcorn cell), highly suggestive of lymphocytic and histiocytic Reed–Sternberg cells (haematoxylin and eosin ×1000).

involvement of the cervix. After two cycles of chemotherapy, the patient died due to renal failure (Mihaljevic et al., 2008). On the other hand, despite remaining a rare event, more cases of non-Hodgkin lymphoma involving the female genital tract have been described in the literature with secondary extension in disseminated disease seen more often than primary disease presentation in the cervix (Upanal and Enjeti, 2011).

In the absence of randomized controlled trials, caused by the rarity of the disease and the low event rate in these patients, the optimal treatment of early-stage NLPHL remains unclear (Nogova et al., 2008). For patients with stage IA and IIA NLPHL, treatment options include extended- or involved-field RT with or without chemotherapy (Nogova et al., 2005). The largest reported experience comes from the Australasian Radiation Oncology Lymphoma Group (Wirth et al., 2005). In this study, the long-term outcome of 202 patients with stage IA–IIA NLPHL treated with EF RT was analyzed. The 15-year overall survival (OS) was 83%, and freedom from progression rate was 84% for stage I disease and 73% for stage II disease. Causes of death were NLPHL, NHL, in-field malignancy or in-field cardiac/respiratory complications. The authors concluded that RT alone is potentially curative in early-stage NLPHL and suggested that involved-field (IF) RT might be as efficacious. A recent analysis of 113 patients with stage I-II NLPHL addressed the question about the optimal RT volume (Chen et al., 2010). In this study, 93 patients received RT alone, 13 received RT with chemotherapy, and 7 received chemotherapy alone. Limited-field, regional-field and EF RT were used. Both progression-free survival and OS did not differ with the extent of irradiated volume. The study also demonstrated the crucial role of RT as inferior outcomes were observed with chemotherapy alone. The adequacy of IF RT in stage IA disease was also demonstrated in a retrospective analysis by the German Hodgkin Study Group (GHSG) (Nogova et al., 2005). In 131 patients treated with EF RT, IF RT or combined modality (CM), the freedom from treatment failure and OS rates were 95% and 99%, respectively. The rate of WHO Grade 3 toxicity was greater with CM treatment. Supported by the aforementioned evidence, our patient was treated with RT alone. A total dose of 50 Gy was delivered, driven by the bulk of her disease and by the well established tolerance of the cervix and vaginal tissue to such a dose.

Two recent studies contribute to defining the role of systemic therapy in early-stage NLPHL. The first is a retrospective analysis of 88 patients treated with RT, ABVD-like chemotherapy followed by RT or ABVD only. The 10-year PFS (91% vs. 65%) and the OS (93% vs. 84%) favoured combined treatment with ABVD (Savage et al., 2011). The second is a phase II study examining the use Rituximab in stage IA NLPHL (Eichenauer et al., 2011). Despite the inferior outcome with Rituximab alone (3-year PFS of 81%), this study helps directing future research that aims at reducing treatment related-side effects in these long-term survivors.

Conclusion

This report describes a rare presentation of a rare disease. The complete response to RT in this patient is consistent with the expected clinical behavior of NLPHL. The optimal management of NLPHL continues to evolve with the search of an effective treatment regimen that carries the lowest long-term side effects.

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Conflict of interest statement
The authors indicated no potential conflicts of interest.

References

Chen, R.C., Chin, M.S., Ng, A.K., Feng, Y., Neuberg, D., Silver, B., et al., 2010. Early-stage, lymphocyte-predominant Hodgkin's lymphoma: patient outcomes from a large, single-institution series with long follow-up. J. Clin. Oncol. 28 (1), 136–141 (Jan 1).

Eichenauer, D.A., Fuchs, M., Pluetschow, A., Klimm, B., Halbsguth, T., Boll, B., et al., 2011. Phase 2 study of rituximab in newly diagnosed stage IA nodular lymphocyte-predominant Hodgkin lymphoma: a report from the German Hodgkin Study Group. Blood 118 (16), 4363–4365 (Oct 20).

IARC, 2008. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Fourth ed. IARC Press, Lyon.

Mihaljevic, B.S., Jovanovic, M.D., Jakovic, L.R., Sretenovic, A.M., Boskovic, D.V., 2008. Hodgkin's lymphoma relapse in the uterine cervix 15 years after the initial cure. Med. Oncol. 25 (2), 245–247.

Morton, L.M., Wang, S.S., Devesa, S.S., Hartge, P., Weisenburger, D.D., Linet, M.S., 2006. Lymphoma incidence patterns by WHO subtype in the United States, 1992–2001. Blood 107 (1), 265–276 (Jan 1).

Nogova, L., Reineke, T., Josting, A., Muller-Hermelink, H.K., Eich, H.T., Behringer, K., et al., 2005. Lymphocyte-predominant and classical Hodgkin's lymphoma–comparison of outcomes. Eur. J. Haematol. Suppl. (66), 106–110 (Jul).

Nogova, L., Rudiger, T., Engert, A., 2006. Biology, clinical course and management of nodular lymphocyte-predominant hodgkin lymphoma. Hematology Am. Soc. Hematol. Educ. Program 266–272.

Nogova, L., Reineke, T., Brillant, C., Sieniawski, M., Rudiger, T., Josting, A., et al., 2008. Lymphocyte-predominant and classical Hodgkin's lymphoma: a comprehensive analysis from the German Hodgkin Study Group. J. Clin. Oncol. 26 (3), 434–439 (Jan 20).

Savage, K.J., Skinnider, B., Al-Mansour, M., Sehn, L.H., Gascoyne, R.D., Connors, J.M., 2011. Treating limited-stage nodular lymphocyte predominant Hodgkin lymphoma similarly to classical Hodgkin lymphoma with ABVD may improve outcome. Blood 118 (17), 4585–4590 (Oct 27).

Shimabukuro-Vornhagen, A., Haverkamp, H., Engert, A., Balleisen, L., Majunke, P., Heil, G., et al., 2005. Lymphocyte-rich classical Hodgkin's lymphoma: clinical presentation and treatment outcome in 100 patients treated within German Hodgkin's Study Group trials. J. Clin. Oncol. 23 (24), 5739–5745 (Aug 20).

Upanal, N., Enjeti, A., 2011. Primary lymphoma of the uterus and cervix: two case reports and review of the literature. Aust. N. Z. J. Obstet. Gynaecol. 51 (6), 559–562 (Dec).

Wirth, A., Yuen, K., Barton, M., Roos, D., Gogna, K., Pratt, G., et al., 2005. Long-term outcome after radiotherapy alone for lymphocyte-predominant Hodgkin lymphoma: a retrospective multicenter study of the Australasian Radiation Oncology Lymphoma Group. Cancer 104 (6), 1221–1229 (Sep 15).